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MILTON B. ROSENBLATT

THE INCREASE IN LUNG CANCER:
EPIDEMIC OR ARTIFACT

(Letter to Federal Trade Commission)

1005142041

Source: https://www.industrydocuments.ucsf.edu/docs/mynk0000

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NEW YORK 28, N. Y.
RHINELANDER 4-3468

May 15, 1967

Mr. F. W. Irish, Chief
Division of Scientific Opinions
Bureau of Deceptive Practices
Federal Trade Commission
6th at Pennsylvania Avenue
Washington, D.C. 20580

Re: Bureau of the Budget
No. D56S 67004
File 662 3108

Dear Sir:

In compliance with your request, I am presenting a summary of my views on the cautionary regulations concerning cigarette smoking. I have been intently interested in pulmonary diseases for 35 years, have written two books and some 50 scientific articles on the subject, and believe that the conclusions of the Advisory Committee to the Surgeon General were unwarranted. I should also like to submit that the report of the Committee was biased in its omission of a plenitude of data challenging the etiologic relationship between smoking and disease.

It is my firm conviction that the statistical association between smoking and lung cancer is not proof of a causal relationship and that there is sufficient evidence indicating that the increase in lung cancer is due to improved diagnostic techniques and not exposure to smoking.

I have prepared this extensive review for your consideration so that you may realize that the subject is far more involved than is indicated in the authoritarian Report of the Advisory Committee. During recent years, research on lung cancer has yielded much valuable information but we are still a long way from establishing etiologic relationships. The search for scientific truth will not be advanced by legislative action based on illusory medical judgments.

Respectfully submitted,

Milton B. Rosenblatt

Milton B. Rosenblatt, M.D.
Associate Clinical Professor of Medicine
New York Medical College

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THE INCREASE IN LUNG CANCER: EPIDEMIC OR ARTIFACT

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The vast increase in lung cancer in the past three decades has nurtured the concept that this is a neoteric disease produced by exposure to recently introduced carcinogenic substances. It its 1966 report, the National Advisory Cancer Council stated that lung cancer was a rare disease fifty years ago and that the rise in lung cancer deaths had assumed epidemic proportions. This concept based primarily on data derived from death certificates, has been widely publicized and has prompted official agencies to recommend legislative remedial action.

The differentiation between the apparent and absolute increase of a disease requires a perspective that encompasses more than an assessment of statistical data. The rapid rise of a disease coincident with advances in diagnostic techniques has occurred many times in the course of medical history. During the last decade of the 19th century when the marked increase in cancer deaths in England was attributed variously to parasitic infestation, meat consumption, and excessive rainfall, King and Newsholme (1) observed prophetically in 1893 that whenever a cancer became diagnostically accessible, the incidence automatically increased. There are many facets of the lung cancer problem that challenge the validity of the epidemic concept. These include (I) Historical considerations, (II) Progress in diagnosis, (III) Simulation of lung cancer by metastatic tumors, (IV) The paradoxical trend of lung cancer mortality, and (V) The biologic features of lung cancer.

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I. HISTORICAL CONSIDERATIONS

It is not generally realized that the first definitive description of the pathology of lung cancer appeared in 1815 in an article by Laënnec (2), the inventor of the stethoscope. There were even earlier references to the subject in the writings of Morgani (3), van Swieten (4), Baille (5), Hey (6), and Abernathy (7) but these were only incidental. In 1819, Laënnec's (8) classic treatise on auscultation was published in France and translated in England by Forbes (9) in 1821. The book aroused considerable interest in both lung cancer and the possibility of clinical recognition by physical diagnosis. Within two decades a literature reflecting considerable experience had made its appearance in both countries.

Lung Cancer in England

As early as 1837, sufficient clinical data had accumulated to provide William Stokes (10) with material for a chapter on cancer of the lung for his book on diseases of the chest. The author's observations on physical findings and the sequelae of bronchial obstruction were astute and established diagnostic criteria that are currently utilized. In 1838, Hare (11) described a syndrome associated with apical lung cancer that was rediscovered as the "superior pulmonary sulcus tumor" in 1932 in an article (12) in the Journal of the American Medical Association. A report by Hughes (13) in 1841 emphasized the importance of postmortem confirmation and the clinical manifestations

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of metastases. MacLachlan (14) in 1842, stressed the paucity of pathognomic clinical features and the problems in differential diagnosis. Walshe (15) in 1843, in his book on physical diagnosis of the lungs, depicted lung cancer as a disease occurring predominantly in males and in older age groups, an observation repeated many times and, in recent decades, attributed to carcinogenic inhalents.

There were two items published in 1843 that depicted the growing interest and general awareness of lung cancer. The first was an editorial comment in the Dublin Journal of Medical Science in which the author of an article was rebuked for not realizing that the case reported as "lardaceous schirrhoma" should have been properly diagnosed as cancer of the lung. The other item was a report in the April 1843 issue of the British and Foreign Medical Review of five recently published articles on lung cancer. The writer apologized for his limited presentation of a subject that had evoked increasing interest and recognition, emphasized that lung cancer occurred far more frequently than previously suspected, and concluded with a plea for greater clinical differentiation from the other pulmonary diseases that it resembled.

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In 1844, Burrows (16) described the superior vena cava syndrome caused by metastases from the lung to the mediastinal lymph nodes. Graves (17), an outstanding clinician and lecturer, emphasized the insidious onset of the disease in his

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textbook in 1848. In the succeeding decade there was developed a distinct awareness of the significance of the histologic findings. Articles, in 1857, by Quain (18), Cockle (19), Mayne (20), and Pitman (21), respectively, included detailed morphologic descriptions of the tumor cells, intra-alveolar propagation, and the patterns of vascular invasion. As autopsy studies became more detailed it became apparent that lung cancer had to be carefully differentiated from visceral tumors metastasizing to the lung and this was emphasized in articles by Budd (22), in 1859, Begbie (23), in 1860, and Page (24), in 1862.

There was an extraordinary interest in the subject during an era in which a positive diagnosis could be established only by autopsy. Many cases were published in the Transactions of the Pathological Society of London and a report by Leared (25), in 1870, referred to a Committee on Morbid Growths which had to certify each case before publication. Walshe (26), in 1871, contributed another book on diseases of the lungs in which were tabulated the various clinical features of lung cancer based on data derived from a collected series of 136 cases. In the same year Reynold's System of Medicine contained a comprehensive chapter on lung cancer by Beigel (27) who presented the subject with all the customary formal headings found in a standard text. Bennett (28), in 1872, referred to 39 cases of lung cancer in his personal experience in the famous Lumleian lectures in the British Medical Journal and in his book, Intrathoracic Growths.

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In the latter years of the 19th century a high level of interest in lung cancer prevailed in England sustained by successive reports in the issues of the Transactions of the Pathological Society of London and in other British journals. A case report by Moore (29), in 1881, described cerebral metastases secondary to lung cancer confirmed by histologic examination. The implications of this study were, unfortunately, not realized for many decades resulting in numerous surgical explorations for brain tumors subsequently proven secondary to unsuspected lung cancers. Harris (30), in 1892, made a study of lung cancer in the City of London Hospital and in St. Bartholomew's Hospital with the conclusion that the disease had become a fairly constant cause of hospitalization and had provided a significant proportion of the autopsies. An article by West (31), in 1897, in the St. Bartholomew's Hospital Reports revealed extensive clinical experience based on observation of 61 cases. The many British publications on lung cancer in the 19th century revealed not only the prevalence of the disease but the intense endeavors in its clinical recognition.

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Lung Cancer in France

Laënnec's studies on lung cancer evoked considerable interest among his contemporaries. As early as 1821, Andral (32) realized that a technique for clinical confirmation would be valuable and suggested examination of the sputum for fragments of tumor tissue. Bouillaud (33) (34), in articles published in

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1826 and 1830, respectively, correlated the symptoms and physical signs with the pathologic findings. He also speculated on the etiologic role of antecedent pulmonary inflammation. Heyfelder's (35) presentation on lung cancer in 1837 was given an award by the Medical Society of Toulouse. In the same year the fourth edition of Laënnec's book was published and it included almost as much discussion on lung cancer in the editorial footnotes as had been presented in the original text.

Awareness of the necessity of differentiation between primary lung cancer and secondary growths in the lung was apparent in Bayle's (36) authoritative book on cancer published in 1839. Problems in differential diagnosis were further clarified in succeeding years in articles by Arnal (37) in 1844, Lebert (38) in 1845, Bleu (39) in 1846, and Monneret and Fleury (40) in 1846. The latter contribution was of particular interest because of its comprehensive discussion of the subject and its inclusion of a considerable bibliography. The importance of autopsy confirmation was stressed by Descroizilles (41) in 1860.

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In the second half of the 19th century an interesting phenomenon was noted in the French publications. The disease had originally been called encéphaloïdes by Laënnec because of its gross resemblance to brain tissue. With the development of greater interest there followed a gradual abandonment of the name descriptive of the pathologic findings and emergence of the clinical

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entity, cancer du poumon. (Replacement of the term, encephaloid, by lung cancer had occurred even earlier in England). By 1861, sufficient clinical and pathologic data had become available in France to enable Aviolat (42) to publish a comprehensive review of the subject in a 95 page monograph.

In the period, 1870-1900, the number of publications reflected both clinical awareness and prevalence of the disease. Jaccoud (43) had written extensively on the subject in various journals and in 1872 provided an excellent discussion in his book on internal pathology. In 1873, Camo-Abden (44) presented a doctoral thesis on lung cancer. The wider use of the term, cancer primitif du poumon, attested to further concern with diagnostic accuracy. One of the outstanding writers of the era was Barié (45) whose article in 1889 contained approximately 200 references. Other significant French contributions were furnished by Auvard (46) in 1882, Muselier (47), Hautecoeur (48), and Ménétrier (49) in 1886, Bouygues (50) in 1888, Boix (51) and Spillman and Haushalter (52) in 1891, Archard (53) in 1893, Bernard and Vermorel (54) in 1894, Leópold-Lévi (55) in 1895, and Szelagonski (56) in 1900.

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Lung Cancer in Germany

The clinical interest in lung cancer manifested by the English and French physicians in the first half of the 19th century was apparently not shared by their German contemporaries

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as evidenced by the paucity of publications and references. Between 1839 and 1841 there were reports by Cless (57), Herzog (58) and Osius (59) but they were not of great importance. More informative contributions of the era were a translation of Heyfelder's (35) 1837 article in France and a case study by Canstatt (60) in 1840. The latter was of particular significance because it used the clinical term, lungenkrebs, the counterpart of the English, lung cancer, and the French, cancer du poumon. The report also implied an awareness of the problems in differentiating between primary and secondary lung cancer in its emphasis that the contralateral lung was "gesund". In 1847, a most detailed study was presented by Koehler (61) in an inaugural dissertation. Clinical manifestations of the primary lesion and metastases were carefully described and there was considerable discussion of the histologic findings.

The most significant German contributions to our knowledge of lung cancer came from the pathologists in the latter half of the century. With the advent of Virchow's doctrine of cellular pathology, interest in histogenesis was intensified. Waldeyer's (62) studies on the origin of carcinoma from epithelial tissue paved the way for the establishment of primary lung cancer as a tumor arising from the columnar cells of the bronchial mucosa. Previously, English authors (Beveridge (63), Martin (64), Powell (65), Salter (66), Beale (67)) had noted intrabronchial tumor masses but had not identified them with the site of origin.

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Ribbert (78), in 1896, cautioned against such conclusions. In 1898, Simmonds (79) wrote a comprehensive summary of the histology of lung cancer which included a discussion on metaplasia. Schwalbe (80), in 1897, contributed an authoritative article to a medical encyclopedia which contained an exhaustive bibliography on lung cancer. During this period, the problems of differentiating, pathologically, between primary and secondary lung cancer were also well recognized in articles written by Hellendall(81) and Lenhartz (82) in 1899.

Lung Cancer in the United States

The subject of lung cancer evoked little interest in this country until the latter half of the 19th century. King (83) found the earliest recorded case, in 1842, in the necropsy records of the Massachusetts General Hospital. In 1850, the New York Journal of Medicine contained a fairly comprehensive article on many phases of the subject by MacDonnell (84). Storer (85), in 1851, reported another case from the Massachusetts General Hospital and a case report by Lehlbach (86), in 1870, in the Transactions of the Medical Society of New Jersey referred to microscopic examination of the sputum. Delafield (87), pathologist at Roosevelt Hospital, New York City was apparently well aware of the disease. In his "Case reports of tumors of the lung, 1868-1888", are recorded, in his handwriting, protocols of cases of primary cancer of the lung autopsied by him at the hospital.

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Loomis (88), in 1876, discussed the subject in his lectures particularly emphasizing the differentiation between primary and secondary growths.

During the latter decades of the 19th century, progress in pathology and increased familiarity with the European literature were reflected in a growing interest in lung cancer in the United States. There were case reports by Pepper (89) in 1878, Van Giesen (90) in 1879, and Ripley (91), in 1880. On December 18th, 1880 the Medical Record editorialized on the vast progress of the pathologic studies on lung cancer in Germany and lamented the lack of specific treatment. There were other interesting case studies by Kemper (92) in 1882, Janeway (93) in 1883, and Holland (94) in 1884. Hare's (95) textbook on mediastinal diseases, published in 1889, devoted considerable attention to lung cancer. In 1895, Loomis (96) demonstrated bronchogenic origin of the tumor and intra-canalicular spread to the alveolar structures. LeCount (97), in 1899, contributed an excellent discussion of the cyto-structural findings in lung cancer calling attention to the features of both benign and malignant epithelial proliferation.

The most informative article of the era was contributed by Adler (98) in the New York Medical Journal, February 8th, 1896. The author stated that despite the extensive literature that had accumulated on lung cancer, the textbooks were still treating the subject in a cursory manner. The clinical features

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and histogenesis of the disease were clearly defined with the conviction that improved diagnostic techniques would result in the clinical recognition of far more cases. Adler also suggested wider utilization of the sputum examination and aspiration biopsy and directed attention to the difficulties in differentiating between pulmonary tuberculosis and lung cancer.

It is impossible to estimate the prevalence of lung cancer in the 19th century or even the number of articles on the subject. Research is limited by lack of indices, reports of cases with obscure titles, and inaccessibility of 19th century publications. However, it is significant that more than 350 articles, theses, and dissertations were located (99) and that the bibliographies contained a great many more references. What is most revealing is the sustained clinical interest in this disease during an era when positive confirmation of the diagnosis was possible only by autopsy.

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Increase in Lung Cancer Autopsies

Stokes' (10) observation in 1837 that lung cancer was not a rare disease was confirmed by many later authors but it was not until the latter decades of the century that statistical considerations were made possible by the intense interest in the subject at the German pathologic institutes. Feilchenfeld (100), in 1901, noted a progressive increase in lung cancer at the Urban Hospital, Berlin, and similar observations were made

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at the Pathologic Institute of Munich by Rieck (101) in 1904. Feldner (102) reviewed the autopsy material at the Pathological Institute of Göttingen between the periods 1852-1879 and 1880-1908 and found incidence of lung cancer among total autopsies had increased from 0.05 per cent to 0.14 per cent. A later study at the same institution by Simmross (103) showed a rise in incidence to 0.45 per cent within the next few years.

The correlated data of Reinhardt (104), Wolf (105), and Junghanns (106) from the Friedrichstadt Hospital in Dresden showed that between the periods 1852-1876 and 1893-1912 the proportion of lung cancers to total cancers had risen from 0.92 per cent to 6.46 per cent and in the period 1913-1927 up to 10.73 per cent. Kikuth (107) reported a ninefold increase in lung cancer at the Eppendorfer Krankenhaus between the periods 1889-1899 and 1900-1911. At the Municipal Hospital in Riga, Hampeln (108) found that the proportion of lung cancer to total cancers had risen from 4.0 per cent in the period 1885-1894, to 12.5 per cent in the period 1895-1899 resulting in an increase of 210 per cent before the turn of the century. 1005142056

The increase in lung cancer autopsies was very evident in the early decades of the 20th century as knowledge of the pathology of the disease became more widespread. At the Neukölln Hospital in Berlin, Kuhn (109) found that between 1909 and 1924 the autopsy incidence had risen from 0.33 per cent to 1.83 per cent. In Zurich, Probst (110) noted that the autopsy

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incidence of lung cancer had increased from 0.11 per cent in the years, 1906-1910, to 0.97 per cent in 1921-1925. Peters (111) studied the lung cancer data at Moabit and Urban Hospitals in Berlin for the period 1895-1931. There were 37,858 autopsies of which 3,957 were carcinomas and 313 were cancers of the lung. In the period 1895-1922 the autopsy percentage was 0.7 per cent; in the period, 1922-1927, it was 1.7 per cent and in 1927-1931 it had risen to 2.6 per cent. Eichengrun and Esser (112) noted a threefold increase at the Augusta Hospital in Cologne between the periods 1902-1910 and 1919-1926. At the Pathologic Institute of Heidelberg, Katz (113) found a twofold increase between the periods 1906-1910 and 1921-1925 and a similar increase was observed by Lipschitz (114) at the Charity Hospitals in Zwickau between the periods 1909-1913 and 1924-1928.

There were divided opinions as to the significance of the increase with speculation on the etiologic role of inhalent irritants, influenza, and tuberculosis. There was also the conviction that the increase was a reflection of progress in pathology. Karrenstein (115) in 1908, reviewing the material at the University of Berlin, emphasized the unreliability of previous records, and stated that greater precision in autopsy examinations had yielded more diagnoses of lung cancer among cases previously classified as pneumonia, lung abscess, or metastatic disease. Adler (116) in 1912, in his classic monograph on primary lung tumors, stated that the official mortality statistics on lung cancer were totally unreliable and that the increased incidence in the latter decades of the 19th century and

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the early years of the 20th century was the result of more meticulous histologic examination of autopsy material. Retrospective studies from Basel in 1925 by Staehlin (117), from Hamburg in 1926 by Brechwoldt (118), and from Innsbruck in 1935 by Sitsen (119) also concluded that the lung cancer increase was more apparent than real, the latter author noting that in addition to greater diagnostic accuracy in autopsies there had also occurred a change in autopsy material based on more selective hospital admissions. Another factor responsible for the increase in lung cancer was the observation by Barnard (120) in 1926 that cases previously diagnosed as sarcomas were, in actuality, oat cell carcinomas. Inasmuch as this histologic type and its variants comprise a significant proportion of all lung cancer autopsies, the recognition of this tumor automatically produced an increase in the incidence of the disease.

Fischer, in the 1931 edition of Henke and Lubarsch, listed almost 4,000 cases of lung cancer with very few American contributions. The increase in lung cancer autopsies became evident in the United States approximately three decades after it had been observed in Europe with reports by Jaffé (121), Halpert (122), and King (83). The obvious explanation for the disparity lies in the lag in the development of pathological experience in this country. The only alternative explanation is that the "epidemic" occurred first in Europe and then took 30 years to cross the Atlantic Ocean. Sudden increases of a

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disease concomitant with increased knowledge is not an unusual phenomenon in pathology or clinical medicine. Autopsies have been performed on cases of tuberculosis since the days of Hippocrates but it was only in the 1930's that pathologists became aware of endobronchial involvement and within the span of a few years it was recognized as one of the most common and important complications of pulmonary tuberculosis.

II. PROGRESS IN DIAGNOSIS

The inherent characteristics of lung cancer, namely, the insidious onset, the variability of physical signs, the resemblance to other pulmonary diseases, and the inaccessibility to direct examination contributed to very slow progress in clinical detection of the disease. For more than a century, the autopsy remained the chief source of diagnostic confirmation. Of 178 cases collected by Sehrt (123) in 1904, only 6 had been recognized during life. It was not until the 1930's that technical procedures were perfected and made generally available for the clinical diagnosis of lung cancer. The subsequent "epidemic" increase was the inevitable outcome of the utilization of newly acquired diagnostic facilities. The vast extent of progress in the past three decades may be evaluated by reviewing the techniques previously available for the diagnosis of lung cancer.

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Physical Signs

The adoption of a systematic method for the examination of the thorax was a major achievement in clinical medicine. Early 19th century autopsy reports of lung cancer often gave no indication that the lungs had ever been examined during the course of illness. Many English physicians were skeptical of the practicability of the stethoscope and, particularily, of Laënnec's achievements with it. Auenbrugger's (124) discovery of percussion in the 18th century had made little impression on clinical medicine and auscultation might also have been relegated to oblivion had it not been for the teaching influence of certain English and French physicians.

During the first half of the 19th century practically all the classical symptons and signs of lung cancer were fully established with a few embellishments added in succeeding decades. The specific symptoms of the tumor such as cough, hemoptysis, dyspnoea, and stridor were emphasized by Hughes (13), Bell (125), Bouillaud (34), and Heyfelder (35). The neurologic and vascular syndromes produced by extrapulmonary metastases were described by MacLachlan (14), Hare (11), Burrows (16), Moneret and Fleury (40), and Lanceraux (126). The earliest criteria for the physical diagnosis of lung cancer were developed by Stokes (16) and Graves (17) who identified unilateral dullness and absent breath sounds with bronchial obstruction and alerted

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their contemporaries to the significance of mediastinal obstruction in differentiating lung cancer from tuberculosis, pneumonia, and pleurisy. Their observations had also revealed that the physical findings in the thorax were dependent on the size and location of the tumor.

The problem of differentiating lung cancer from other pulmonary diseases by physical diagnosis plagued physicians throughout the 19th century and the quest for the elusive characteristic physical finding continued well into the 20th century. Béhier (127), in 1867, believed he had discovered it in a respiratory murmur which he called "cornage"; Woillez (128), in 1870, described a particular percussion note, "tympanisme thoracique"; Hesse (129), in 1878, identified wheezing with lung cancer; Sée (130), in 1881, emphasized the absence of tactile fremitus; and Witthauer (131), in 1899, relied on thoracic resistance to percussion. In 1912, Adler (116) recommended a variety of tactile maneuvers including "schwellenwerthperkussion", plessimetre percussion, and orthopercussion, and Fishberg and Steinbach (132), in 1921, stressed the association of flatness and absent breath sounds.

An experience in lung cancer developed in the early decades of the 19th century, the inadequacies of physical diagnosis became readily apparent. In 1842, MacLachlan (14) demonstrated that lung cancer could occur with few characteristic symptoms and with no recognizable signs. Smith-Shand (133),

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in 1875, summarized the diagnostic frustrations of the era in the British Medical Journal with the comment that despite the large number of publications on lung cancer, the disease still baffled the skill of the physician. During the first three decades of the 20th century, the clinical diagnosis of lung cancer was still dependent on physical signs established almost 100 years previously.

The Sputum Examination

The possibility of diagnosing lung cancer by examination of the sputum was nurtured for a century before coming to fruition in the 1940's with the perfection of Papanicolaou's cytologic technique. The early endeavors by Andral (32) in 1821 and Walshe (15) in 1843 involved microscopic study of expectorated tissue fragments, a procedure which met with very little success because of lack of effective staining methods and the infrequent occurrence of tumor tissue in the expectorate. The difficulties in the microscopic examination of sputum did not deter later investigators from pursuing this approach and in 1887, Hampeln (134) demonstrated that lung cancer could be diagnosed clinically by the examination of expectorated tissue.

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The gross characteristics of the sputum were also given considerable attention. Most of the writers on lung cancer were very much impressed with the resemblance of the

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sputum to jelly but there was considerable difference of opinion as to which type was pathognomonic. In England, Stokes (10), Hughes (13), and Burrows (16) found the greatest similarity to red currant jelly; in France, Sée (130) thought that the comparison to raspberry jelly was more fitting; in Germany, Janssen (135) identified the disease with grass-green sputum. The concept of a typical lung cancer sputum was generally accepted throughout the 19th century and perpetuated in textbooks in the early decades of the 20th century.

The first significant cytologic studies on sputum were made in 1895 by Betschart (136) who identified cancer cells as large round cells with over-sized nuclei and keratinized cytoplasm occurring singly or in clusters. In 1899, Hermann (137) established criteria for differentiating between malignant squamous cells and benign squamous epithelium commonly desquamated from the buccal cavity. During the same era, Claisse (138), in France, predicted that the cytologic examination of the sputum would eventually provide the means for the early diagnosis of lung cancer but problems in developing suitable staining techniques delayed utilization of the procedure for several decades. Considerable progress was made by Dudgeon and Wrigley (139) in 1935, Wandall (140) in 1938 and Gowar (141) in 1943 but the most important step was the application of Papanicolaou's gynecologic staining technique to the examination of sputum smears.

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The introduction of the "Pap" smear and its wide utilization since 1946 added immeasurably to the procedures available for the diagnosis of lung cancer. The technique was readily acquired by pathologists and, in many institutions, the large number of daily examinations requested necessitated the relegation of screening to non-medical personnel. Reports of accuracy have varied with investigators but Papanicolaou (142) found the procedure confirmatory of lung cancer in 90 per cent of his cases and, of particular value, in small tumors not visible on x-ray or accessible to bronchoscopic visualization. It is difficult to assess the role of the "Pap" smear in the increase in lung cancer certification, but it is very apparent that a procedure that is readily performed, widely utilized, and applicable to patients in all stages of the disease, would result in the diagnosis of a great many more cases than was possible prior to 1946.

The X-ray Examination

On November 8th, 1895, Wilhelm Roentgen, college president and amateur physicist, accidently discovered in the basement laboratory of his home that an electrified Crooke's vacuum tube emitted a greenish light capable of penetrating flesh. The early experiments involved chiefly the osseous structures but it was soon realized that the x-ray had possibilities in the examination of the thorax and its contents. In

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1901, Weinberger (143) succeeded in producing x-ray pictures of the lung on photographic plates. His article in the Zeitschrift für Heilkunde showed illustrations of lung cancer and photomicrographs of the tumor specimens proving that the diagnosis had been confirmed at autopsy. Further progress in the diagnostic radiology of lung cancer was made by Otten (144) in 1906 but attempts to popularize this form of investigation met with little enthusiasm because of technical difficulties and personal hazards to both patient and physician.

In the United States, Williams (145) was the most active of the early pioneers in chest radiography. His studies demonstrated the usefulness of the x-ray in the differential diagnosis of pulmonary diseases but the importance of his findings was not generally recognized. In 1916, it was proposed at a meeting of the American Sanatorium Association that the x-ray be used in the classification of pulmonary tuberculosis but this suggestion was not finally adopted until 1920. A considerable reluctance to the acceptance of x-ray findings resulted from the numerous failures in developing a standardized technique for x-ray of the chest. Most of the films were overexposed and the images distorted due to lack of proper tube distance and respiratory movements. However, interest in the procedure was sustained by Edison's perfection of the fluoroscope which made it possible to visualize the heart and lungs even though the image could not be successfully recorded om plates.

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The x-ray apparatus of the 1920's was a crude instrument with exposed parts capable of producing shocks, burns, and malignant changes. Its wide utilization was limited by its inherent defects and the lack of knowledge regarding its potentialities. As the decade progressed much progress was made in the production of shockproof machines, replacement of glass photographic plates by celluloid film and standardization of x-ray techniques. Sectional radiography was introduced in 1933 as a supplementary diagnostic procedure. In the late 1930's machines began to be produced for mass chest surveys and during recent decades photofluorographic units requiring little technical skill have been installed in countless hospitals, clinics, and health centers screening large segments of the population for lung cancer and other pulmonary diseases. The repeated exposure of millions of adults to x-ray examination has been concurrent with the rapid increase in the diagnosis of lung cancer.

Bronchoscopy

In the closing years of the 19th century Killian (146)(147), devised an instrument by means of which he could directly visualize the bronchi and reported his findings on lung cancer in the Berliner klinische Wochenschrift in 1900. The instrument achieved some degree of popularity in Germany and Mann (148), in 1911, published an atlas with illustrations depicting the diagnosis of bronchogenic carcinoma and other

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diseases involving the bronchi. However, technical difficulties and unwarranted anxieties regarding the hazards of the procedure delayed widespread use of bronchoscopy for two decades.

The greatest impetus to bronchoscopy in the early decades of the 20th century was provided by Jackson (149) (150) who established that the procedure was practicable and of invaluable assistance in diagnosis. His clinic in Philadelphia was world famous and by 1930 he had diagnosed 486 cases of lung cancer. The contrast between Jackson's achievements and other means of diagnosis available during that era was very apparent inasmuch as the total lung cancer deaths reported for the entire United States in 1930 was only 2,837. The awareness, in the 1930's, that endobronchial tuberculosis was a common complication of pulmonary tuberculosis led to a more general use of bronchoscopy in tuberculosis sanatoria and hospitals and subsequently, in general hospitals. It was soon realized that the procedure had few contra-indications and was applicable to all pulmonary problems.

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In the early decades of this century, bronchoscopic examinations were usually performed by otolaryngologists but in more recent years, the examinations have been also done by thoracic surgeons thereby expanding the availability of the procedure. The vast increase in bronchoscopic examinations is very evident in Smither's (151) report from the Brompton Hospital where only one bronchoscopy was done prior to 1925 and over 800

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0900

annually by 1952. During the past three decades bronchoscopy has been frequently performed in all hospitals and has made it possible to diagnose lung cancer in cases presenting clinically as pneumonia, tuberculosis, lung abscess, or pleural effusion. It would be unrealistic not to relate the widespread use of an effective investigative technique with the increase in the number of cases diagnosed.

Thoracic Surgery

At the turn of the century, Benda (152), a German pathologist with particular interest in pulmonary disease, stated that the inaccessibility of the lung precluded the possibility of surgical therapy for lung cancer. This dour prediction did not deter a number of surgeons including Brauer (153), Friedrich (154), Sauerbruch (155) and Willy Meyer (156) from attempting surgical exploration of the thorax. Lenhartz (157) in 1898, reported one successful lobectomy for lung cancer with survival for a year and a half but little progress was made in the succeeding decade. Adler (116) in 1912 recommended exploratory thoracotomy for diagnosis but was very pessimistic about the possibilities of surgical therapy for lung cancer except as a palliative procedure.

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Progress in exploratory thoracotomy for lung cancer followed the advances in surgery for non-malignant disease. Heidenhain (158) in 1901 reported the first successful lobectomy

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

for bronchiectasis and by 1925, there were 85 cases in the literature. However, the operative mortality rate in reported series (159) approximated 60 per cent. Between 1925 and 1935, refinements in technique introduced by Shenstone and Janes (160) and others reduced the surgical hazards considerably and by 1940, experienced surgeons such as Churchill (161) reported mortality rates of less than 4 per cent for lobectomy in non-malignant disease. The first successful pneumonectomy for bronchiectasis was performed by Nissen (162) in 1931.

In 1933, Graham (163) provided the greatest stimulus to the surgical therapy of lung cancer in his report of the first successful pneumonectomy in the Journal of the American Medical Association. It is of historical interest that the patient, a physician, was able to resume his practice and survived more than 25 years. Progress in thoracic surgery was greatly enhanced by experience in World War II which inspired many surgeons to pursue the specialty in civilian life. In the 1940's the thoracic surgeon had many advantages over his predecessors in the form of better anesthesia, antibiotic coverage, blood bank facilities, and newly developed concepts of pulmonary physiology.

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The perfection of surgical technique was not correspondingly reflected in increased surgical cures of lung cancer but exploratory thoracotomy vastly increased the opportunities for diagnosis of the disease. As early as 1949, Johnson, et al(164)

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

reporting on 384 patients with varied pulmonary diseases found 123 cases of lung cancer of which 60 (49 per cent) were diagnosed only by thoracotomy. During the past two decades, exploratomy thoracotomy has become a routine diagnostic procedure in practically all hospitals with relatively few contraindications because of the low operative mortality. It has thus been possible to increase the incidence of lung cancer among cases undiagnosable by other means.

Ancillary Procedures

Lymph node biopsy has become an increasingly popular procedure for differential diagnosis in patients with obscure pulmonary lesions who are unsuitable for exploratory thoracotomy. The biopsies include accessible cervical nodes, scalene nodes, and more recently, mediastinal nodes. The relationship between supra-clavicular adenopathy and abdominal malignancy was established by Virchow in the mid 19th century but the pathways of lymphatic spread from the lung to the neck were not clearly defined until Rouviére's (165) studies in 1938. In 1949, Daniels (166) demonstrated the potentialities of scalene node biopsy and since then this procedure has been performed thousands of times. Gondos and Reingold (167) in a study of 175 proven cases of lung cancer, found 70 (40 per cent) positive scalene lymph node biopsies. In recent years biopsy of mediastinal lymph nodes has been used as a more direct diagnostic approach with considerable

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

success. It is pertinent that the wide utilization of lymph node biopsy has occurred during the past two decades when the rise in lung cancer has been so striking.

Aspiration biopsy of the lung has been practiced since the 19th century. The procedure was first introduced by Krönig (168) in 1887 under the name of "Probepunktion" (probatory puncture) and also used in Germany by Hellendal (81) in 1889. In the United States, Adler (169) recommended its routine adoption in 1896 but the inaccuracy of results and hazards of spread of the tumor limited its usefulness. In recent years, more accurate localization and specially designed aspiration needles (170) have led to a revival of interest, particularly, in cases not amenable to other forms of diagnostic investigation. A study of lung cancer deaths by Haenzel, et al (171) in 1962 revealed that out of 1,820 cases with microscopic confirmation there were 112 (6.2 per cent) in which the diagnosis had been confirmed by aspiration biopsy. Aspiration of pleural fluid is also used to establish the diagnosis of lung cancer. Prior to the introduction of Papanicolaou's staining technique the procedure consisted of the usual preparation of a cell block from the centrifuged specimen. In recent decades the pleural fluid has also been subjected to cytologic study.

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An unrelated diagnostic procedure, the culture of sputum and gastric aspirates for tubercle bacilli, has also led to detection of more cases of lung cancer. Thirty years ago, the

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

diagnosis of pulmonary tuberculosis would be readily accepted on the basis of x-ray findings even if the sputum were negative for tubercle bacilli. In recent years, the finding of negative cultures in cases suspected of pulmonary tuberculosis has made it obligatory to initiate further investigative procedures.

Accuracy in Diagnosis

It is impossible to ascertain with certainty how much of the recent increase in lung cancer is genuine and how much may be attributed to advances in investigative techniques. Willis (172), contrasting the modest increase in the autopsy incidence of lung cancer in England in the period, 1929-1950, with the tenfold increase in registered deaths, inferred that practically all of the increase was the result of diagnostic progress. There is much evidence to support this contention.

In 1920, there were 956 lung cancer deaths reported in the United States. At that time, the prevailing methods of diagnosis consisted of clinical intuition, physical examination, and the autopsy. During the next decade, the x-ray examination began to be widely used in hospitals and in 1930, there were 2,357 lung cancer deaths reported. Between 1930 and 1940, bronchoscopy was added to the diagnostic routine and thoracotomy was beginning to emerge as a relatively safe surgical procedure. The total lung cancer deaths in the United States rose to 7,121, in 1940.

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

The succeeding years were characterized by the introduction of the cytological examination of the sputum and bronchial aspirates, the widespread use of exploratory thoracotomy and surgical resection, and mass x-ray examination of the population. In 1950, the total number of lung cancer deaths reported was 18,313. Since then, the tremendous awareness of lung cancer has resulted in an intensification of diagnostic investigation in all pulmonary disorders with particular emphasis on biopsy procedures leading to histologic confirmation. There has also occurred a considerable degree of selectivity in autopsies because of the general interest in lung cancer. The association of public anxiety, medical zeal, and readily available diagnostic facilities has been reflected in a further striking increase of lung cancer deaths with 36,420 reported in 1960, and 50,000 deaths estimated for 1966. The rise in reported lung cancer deaths paralleled the utilization of clinical diagnostic techniques which were virtually non-existent in the early decades of this century.

Statistical studies on the correlation between clinical diagnosis of lung cancer and autopsy confirmation show very clearly how much progress has occurred since the introduction of modern investigative techniques. In a collected series of 178 cases confirmed by autopsy between the years, 1887 and 1900, Sehrt (123) found that only 6 (3.4 per cent) had been diagnosed correctly during life. Ferenczy and Matolcsy (173)

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

found 18 (22.5 per cent) out of 80 cases diagnosed clinically between 1907 and 1916 and 44 cases (28.5 per cent) out of 150 between 1917 and 1925. A series of 1,070 cases between 1939 and 1949 collected by Farber (174) from 19 hospitals showed a 39 per cent accuracy in clinical diagnosis. During the succeeding decade there was considerable progress in clinical acumen. Halpert (175) (176) reporting on 363 autopsy cases of lung cancer between the years 1949 and 1958 found that 80.7 per cent had been diagnosed correctly during life. The diagnosis had been made by exploratory thoracotomy and/or resection in 88 cases; by bronchial biopsy in 50 cases; by lymph node biopsy in 50 cases; by skeletal muscle or skin biopsy in 25 cases; by needle biopsy of liver or lung in 12 cases; by craniotomy or laparotomy in 11 cases; and by cytologic examination of sputum, bronchial aspirate, or pleural fluid in 15 cases. There were 42 cases without histological or cytologic confirmation in which the diagnosis was made by x-ray examination.

The gradual improvement in diagnostic accuracy during the past 50 years was not limited to the cases confirmed by autopsy which account for only a small proportion of the increase in lung cancer. Haenzel, et al (177) found only 656 (27.5 per cent) of 2,381 cases confirmed by microscopic autopsy; the remainder of the cases had been diagnosed by bronchial, lymph node, or aspiration biopsy; excision of surgical specimen; x-ray examination, or other means. The implication is very clear. It would have been impossible to diagnose the non-autopsied cases a few

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

decades ago because the methods currently utilized were not available. The assumption that there has been an epidemic rise in lung cancer is, therefore, pure conjecture.

III SIMULATION OF LUNG CANCER BY METASTASES

The widespread utilization of radiology, bronchial and lymph node biopsy, exploratory thoracotomy, and cytology has made it readily possible to detect lung cancer clinically but there are many diagnostic pitfalls inherent in these procedures. Autopsy follow-up has made it increasingly apparent that metastatic tumors may produce findings entirely compatible with the diagnosis of bronchogenic carcinoma.

Magnitude of Problem

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One of the earliest demonstrations of metastases simulating bronchogenic carcinoma was reported by Funk (178) in 1930. The case had been diagnosed as primary lung cancer by bronchial biopsy but postmortem examination revealed a primary carcinoma of the pancreas. In 1935, Farrell (179) reported two cases of malignant melanoma and carcinoma of the endometrium respectively, with bronchial involvement producing the type of massive atelectasis found in bronchogenic carcinoma. Maytum and Vinson (180), in 1936, reported a case of hypernephroma with metastatic ulceration into a bronchus. Peery (181), in 1940, reported three cases of extensive bronchial metastasis and

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

emphasized that malignant involvement of the bronchial mucosa was not an absolute criterion of primary origin. Raine (182), in 1941, found a large papillomatous mass in a bronchus with histologic findings of adenocarcinoma. A subsequent pneumonectomy revealed that the pulmonary tumor had been metastatic to a previously resected carcinoma of the colon.

In 1942, pulmonary metastases from carcinomas of the ovary and thyroid simulating bronchogenic carcinoma were described by Freedlander and Greenfield (183). A case of gastric cancer with metastasis to the left upper lobe was reported by King and Castleman (184) in 1943; the diagnosis of lung cancer had been established by aspiration biopsy and the patient subjected to lobectomy. Leach (185) in 1950 reported three cases of carcinoma of the pancreas erroneously diagnosed as bronchogenic carcinoma; in one of the cases the bronchial biopsy had been positive for lung cancer. In the same year Seiler, et al (186) found that in 17 cases with metastatic bronchial involvement, 10 (59 per cent) had positive bronchial biopsies.

Abbott (187), in 1961, reported 13 cases of endobronchial metastases masquerading as bronchogenic carcinoma. In 1962, Campagna and Greenberg (188) described a case of metastatic carcinoma of the rectum diagnosed as lung cancer by bronchial biopsy. Trinidad, et al (189), in 1963, reported 10 cases of metastatic cancer diagnosed as bronchogenic carcinoma by biopsy or cytologic examination. The subsequent autopsies

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

revealed 4 carcinomas of the pancreas, 3 carcinomas of the kidney, 2 adrenal cancers, and 1 lymphosarcoma. A review of 104 autopsy cases of carcinoma of the pancreas by Lisa, et al (190) in 1964 revealed that 12 cases (12 per cent) had been diagnosed during life as bronchogenic carcinoma; in 9 of the cases there had been histologic confirmation by biopsy. The features of carcinoma of the pancreas favoring simulation of primary lung cancer were the high incidence of metastases to the lung and to the mediastinal, tracheobronchial, and paratracheal lymph nodes. Thoracic metastases occurred most frequently in carcinomas of the tail of the pancreas which remained silent for long periods of time thereby adding to the possibility of erroneous diagnosis.

Bronchiolo-alveolar (alveolar cell) carcinoma has been generally accepted as an adenocarcinoma of the lung characterized by peripheral origin and a distinctive histologic appearance. In 1946, Herbut (191) challenged this concept and reported 6 cases of metastatic lung cancer showing the typical alveolar propagation identified with bronchiolo-alveolar carcinoma. The primary tumors were located in the rectum, colon, pancreas, and gall bladder, respectively. Similar observations were made by Eck (192) in 1955 and Johnsen and Olsen (193) in 1957. In 1961, Rossman and Vortel (194) collected 20 cases of metastatic lung cancer with the bronchiolo-alveolar pattern and added 5 cases of their own. Hewer (195), in the same year, reported 4 cases secondary to carcinoma of the pancreas; in 2 of the cases the

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Source: https://www.industrydocuments.ucsf.edu/docs/tynk0000

primary tumors were very small and had not been detected on the first gross examination of the tissues.

The duplication of the distinctive histologic features of bronchiolo-alveolar carcinoma by metastases from extrathoracic carcinomas has significant clinical importance. Unless there is autopsy exclusion of other primary sites, the diagnosis can not be made with certainty. There has been a progressive rise in the reported incidence of this tumor in the past few decades. In 1942, Neuberger and Geever (196) found only 25 cases in the literature; in 1949, Swan (197) compiled an additional 27 cases and added 9 cases of his own; and in 1957, Eck (198) recorded 337 cases. In 1961, Bell and Knudtson (199) found the tumor to occur in 8 per cent of primary lung cancers. Reports of incidence have varied and the tumor has been diagnosed under many names ranging from malignant pulmonary adenomatosis to peripheral adenocarcinoma. Mimicry of bronchiolo-alveolar carcinoma by metastases makes it impossible to make an absolute diagnosis on the basis of biopsy or resected surgical specimen.

In an attempt to assess the magnitude of the problem of metastatic simulation of bronchogenic carcinoma, Rosenblatt, et al (200), in 1966, reviewed the autopsy protocols and clinical records of 380 cases of extrathoracic carcinoma. Pulmonary metastases occurred in 50 per cent. More than 10 per cent of the extrathoracic carcinomas had been erroneously diagnosed clinically as primary lung cancer with cytologic and/or histologic

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Source: https://www.industrydocuments.ucsf.edu/docs/nyhk0000

confirmation in two-thirds of the cases. Carcinoma of the pancreas presented the greatest source of diagnostic error and carcinoma of the kidney was next in frequency. The other primary sites were breast, adrenal, endometrium, prostate, colon, stomach, thyroid, larynx, ovary, and esophagus. In a recent study of 194 pulmonary malignancies diagnosed by bronchial biopsy, Lemoine, et al. (261) found 101 cases (52 per cent) of metastatic disease, mostly secondary to cancer of the breast and uterus.

Causes of Diagnostic Errors

The factors found chiefly responsible for the erroneous histologic diagnosis of bronchogenic carcinoma were (a) metastatic involvement of the larger bronchi and (b) pleomorphism of the lung and lymph node secondary growths. Invasion of the bronchial wall by way of the subepithelial lymphatics led to the formation of coalescing tumor masses which eventually ulcerated through the epithelium and formed polypoid projections into the lumen. Bronchoscopic visualization revealed a tumor apparently arising from the bronchial mucosa and a biopsy positive for malignancy confirmed the incorrect diagnosis. Metastatic involvement of the bronchi also produced positive findings of cancer cells in the sputum and bronchial aspirates.

Extrathoracic ductal or glandular carcinomas often presented squamoid features in metastatic lesions of the lymph nodes or lungs. Crowding and proliferation of the malignant cells in the new environment produced the effect of cells arranged in sheets giving the appearance of undifferentiated

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squamous carcinoma. These metastatic foci did not have the characteristic features of a true squamous carcinoma such as keratinization or pearl formation but the resemblance was sufficient to cause diagnostic confusion, particularly, in frozen tissue sections. Adenocarcinomas metastasizing to the alveolar structures first proliferated along the walls but eventually filled the alveolar spaces. The ultimate effect was that of a broad sheet of malignant squamous cells in which evidence of metastatic origin was obtainable only by special staining techniques or meticulous search for ductal or glandular structures.

In many instances, the certification of bronchogenic carcinoma on death certificates has been based only on the x-ray examination. This is a major diagnostic pitfall. It is customary to think of pulmonary metastases as presenting bilateral nodular densities, linear striations, or pleural effusions on the x-ray films but metastases may also present as unilateral solitary shadows or atelectatic areas comparable to densities observed in bronchogenic carcinoma. These latter effects are usually produced by involvement of the larger bronchi with endobronchial obstruction.

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Validity of Certification

The vast majority of certifications of lung cancer are not based on autopsy confirmation but on procedures by which it may not be possible to differentiate between primary and

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

secondary lung cancer. The affinity of the lung for metastases therefore creates a large potential for diagnostic error.

In a study of 2,381 lung cancer deaths among white males Haenszel, et al (171) found that 656 (27.5 per cent) of the cases had been diagnosed by autopsy and that 1,725 (72.5 per cent) had been diagnosed by other means. There were only 625 cases (26.2 per cent) diagnosed by biopsy of a surgical specimen. Among the remaining cases the diagnosis was made by bronchial biopsy in 288 (12.1 per cent); by biopsy of a metastatic site in 139 cases (5.8 per cent); and by aspiration biopsy in 112 cases (4.7 per cent). The diagnosis had been made on x-ray evidence, alone, in 418 cases (17.5 per cent). There was also a miscellaneous group of 143 cases (6 per cent) in which the diagnosis of lung cancer was based on autopsy without microscopic examination (35 cases); on clinical findings only (35 cases); and for reasons "not stated" (75 cases).

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In a similar study among white females, Haenszel and Taeuker (177) found that out of 749 cases certified as dying of lung cancer only 134 (18 per cent) had microscopic autopsy confirmation and 615 cases (82 per cent) were diagnosed by other methods. There were 183 cases (24.4 per cent) with biopsy of a surgical specimen; 82 cases (11 per cent) with aspiration biopsy; 63 cases (8.4 per cent) with bronchial biopsy; and 51 cases (6.8 per cent) with biopsy of a metastatic site. There were 171 cases (22.8 per cent) diagnosed by x-ray examinations and 56 cases

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

certified on the basis of "clinical findings only" or reasons "not stated". The remaining 9 cases had autopsies without microscopic examination of the tissues.

The above mortality studies are presumably representative of the procedures used throughout the United States in the diagnosis of lung cancer. They show that approximately one fourth of the white male cases and one third of the white female cases had been certified as dying of lung cancer without any histologic confirmation, whatsoever. It is also evident that among the male cases with histologic examination, almost twice as many had veen validated by biopsy as compared with autopsy; among the female cases with histologic examination, almost three times as many cases had been validated by biopsy.

In a study of death certification of lung cancer in Leeds, Bonser and Thomas (201) found that out of 953 cases, only 267 (28 per cent) were confirmed by autopsy. There were 210 cases (22 per cent) in which the diagnosis was based on clinical histology. There were 456 cases (47.8 per cent) in which the diagnosis was made without any histological confirmation and, in 47 of these, the diagnostic data was limited to history and physical examination. Of considerable interest was a special study of the autopsied cases which showed that 10 per cent had been erroneously diagnosed as bronchogenic carcinoma on the death certificates. If this study is representative of lung cancer certification in England, the vast majority of cases certified as

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Source: https://www.industrydocuments.ucsf.edu/docs/nyml0000

dying of primary lung cancer did not have autopsy confirmation and almost 50 per cent did not have any histological confirmation.

The approximately 300,000 annual deaths from cancer in the United States provide a large potential for the erroneous diagnosis of bronchogenic carcinoma. Many of these diagnostic errors are corrected at autopsy but this information does not affect the official mortality statistics which are usually based on clinical data. There are no procedures readily available for the amending of death certificates nor is modification encouraged by municipal, state, or national authorities. In the customary order of events, the certificate is made out immediately after the death of the patient and the case is processed by the local health department. Time is required for the performance of a meticulous autopsy and, regardless of the final results, the disease is classified as primary lung cancer in the official vital statistics and tumor registries because of the original certification.

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Accuracy in lung cancer mortality data requires a careful study of all biopsy material including resected lungs. The differentiation between primary and secondary lung cancer is often difficult and at times, infeasible. The harried hospital pathologist seldom has the time to scrutinize surgical specimens for stigmata of metastases and is apt to diagnose bronchogenic carcinoma on the basis of squamoid features of the tumor, bronchiolo-alveolar appearance, or endobronchial masses resulting from secondary lymphatic invasion.

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

The autopsy is the most accurate method for confirming the diagnosis of bronchogenic carcinoma but this important procedure is often delegated to inexperienced assistants or residents whose knowledge of the pathologic manifestations of bronchial and pulmonary metastases is very limited. Solitary tumors involving the larger bronchi are readily identified as primary lung cancers without attempting to establish bronchial origin or carefully examining the other organs for possible inconspicuous primary sites. Multiple disseminated lesions are often classified as primary lung cancer because of the failure to establish an extrathoracic primary origin. The validity of mortality data on lung cancer is dependent on the adherence to rigid histologic criteria in both the biopsy and autopsy diagnosis of bronchogenic carcinoma.

In the evaluation of the epidemic rise in lung cancer, three related phenomena should be considered -- (1) the vast majority of cases have been diagnosed by biopsy and x-ray examination, (2) the increase in lung cancer has been concurrent with the widespread utilization of these procedures, and (3) autopsy follow-up has shown that there are many diagnostic pitfalls in these procedures. Biopsy and x-ray examinations have accounted for most of the cases detected during recent decades and have also been responsible for erroneous diagnoses because of the mimicry of bronchogenic carcinoma by metastases from extrathoracic carcinomas.

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

IV THE PARADOXICAL TREND OF LUNG CANCER MORTALITY

The tremendous rise in lung cancer deaths has been accepted by the Surgeon General's Advisory Committee as unequivocal evidence of a true increase in the disease but there are many aspects of the problem that challenge this conclusion. An objective evaluation requires consideration of (1) the difficulties involved in the compilation of comparative statistical data and (2) the trend of lung cancer mortality during the past 35 years.

The collection of annual vital statistics based on information recorded on death certificates was begun in 1900. The original registration area included 10 states, a number of cities in non-registered states, and represented a total population of 30,765,618 (202). Expansion of the registration area was not uniform because of the withdrawal and readmission of previously registered states. In 1905, the registration area included 40 per cent of the population of the United States; in 1915, the area included 68 per cent and in 1925, the area included 90 per cent. Annual mortality data for the whole country have been in existence only since 1933.

Variations in Geographic Distribution

Mortality rates for lung cancer varied among the states and were often directly proportional to the number of years that the states had been included in the Death Registration

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

area. As late as 1949, there were 8 states with significantly higher standardized rates and 19 states with significantly lower standardized rates in comparison with the total United States experience (203) (204). The states that had been registered in 1914 had a much higher rate in 1949 than the non-registered states. It is evident, therefore, that comparable mortality data for the entire United States prior to 1933 are not available. The admission of new states into the registration area had the effect of artificially lowering the lung cancer mortality in the earlier decades.

Geographic variations in lung cancer death rates continued for many years suggesting the implication of factors such as diagnostic sophistication, case finding surveys, and accuracy in certification. Between 1940 and 1950 there existed a wide disparity in age specific death rates among the various regions of the United States with the highest rates recorded in the Middle Atlantic and New England areas and the lowest rates in most of the Central and Northwest areas (205). The lung cancer death rates in 1950 in North Dakota, Arkansas, Idaho, New Mexico, North Carolina, and Utah were approximately one half of those recorded for New York, New Jersey, Maryland, and Delaware. Geographic location was not the only major difference between the areas with high rates and those with low rates. In general, the states with the highest recorded mortality from lung cancer were more industrialized, more urbanized, and had a far greater number of physicians per 100,000 of population than the states

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

with the low rates which were predominantly in agricultural or mountain regions.

There were certain characteristics of the increase in lung cancer between 1940 and 1950 that have an important bearing on the entire problem. The increase in lung cancer mortality was most evident in the states which had the lowest rates in 1940 and the smallest number of physicians. In South Carolina, with 74 physicians per 100,000 of population, the lung cancer death rate rose from 1.9 per 100,000 in 1940 to 8.5 per 100,000 in 1950, an increase of 347 per cent. A similar experience was noted in Arkansas with 94 physicians per 100,000 of population. The lung cancer death rate rose from 2.2 per 100,000 in 1940 to 8.3 per 100,000 in 1950, an increase of 277 per cent. Among states with large numbers of physicians and with relatively high lung cancer death rates in 1940, the increase was far less dramatic. In Massachusetts, with 183 physicians per 100,000 of population, the death rate rose from 10.5 per 100,000 in 1940 to 16.4 per 100,000 in 1950, an increase of 56 per cent. A similar experience was noted in New York with 203 physicians per 100,000 of population where the death rate rose from 13.5 per 100,000 in 1940 to 20.9 per 100,000 in 1950, an increase of 55 per cent.

The above data show some very significant correlations. All the states showed a rise in lung cancer mortality between 1940 and 1950 but the greatest increases occurred in the states with the lowest rates and the smallest physician to

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Source: https://www.industrydocuments.ucsf.edu/docs/

population ratios in 1940. It is very apparent, therefore, that the differences in the magnitude of the increase among the various states was not dependent, per se, on geographic distribution but on the medical facilities available for the detection of the disease. During the decade, 1940-1950, the techniques for diagnosing lung cancer became more and more available to all segments of the country and the disparity in lung cancer mortality among the states began to diminish.

Faulty Certification

Although autopsy studies are not necessarily representative of the population they represent, it is interesting to note that a study by Farber (174) in 1954 revealed that less than 40 per cent of 1,070 cases of lung cancer had been diagnosed prior to autopsy. It is impossible to estimate how many lung cancer cases were undetected in the earlier decades of this century. However, if only a small percentage of the cases certified as dying of tuberculosis or pneumonia had been erroneously diagnosed, the lung cancer mortality rate would have been comparable to current trends.

For many years, tuberculosis and pneumonia comprised the major causes of death attributed to respiratory diseases. In 1900, the crude death rates for respiratory tuberculosis and for pneumonia were, respectively, 180.5 per 100,000. The death rate for bronchitis was 45.7 per 100,000 and for influenza it was 22.9 per 100,000. The other respiratory diseases, combined, had a death rate of 26.7 per 100,000. There were no death rates recorded for lung cancer until 1914. During successive years, the death rates for all respiratory diseases declined and in 1914 the crude death rate for respiratory

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

tuberculosis was 123.1 per 100,000 and for pneumonia, it was 127.0 per 100,000. The death rates for influenza, bronchitis, and other respiratory diseases also showed striking reductions.

The overall crude death rate of lung cancer in 1914 was 0.6 per 100,000 and in 1950, it was 12.5 per 100,000. According to the calculations of Gilliam (206), the following percentages of diagnostic error in deaths attributed to tuberculosis and other respiratory diseases would be necessary for the 1914 lung cancer mortality to equal that of 1950. Among the deaths attributed to tuberculosis, faulty certification in 11.2 per cent of the males and 2.8 per cent of the females would have resulted in equalization of lung cancer mortality between 1914 and 1950. When pneumonia and the various other respiratory diseases are considered as a group, an error of 5.0 per cent among the males and 1.1 per cent among the females would also have resulted in parity.

The consequences of faulty certification may also be contemplated by postulating the effect of a specific percentage of diagnostic error. In 1914, the age-adjusted death rate of lung cancer in white males over 35 years of age was 0.8 per 100,000. If 10 per cent of the deaths attributed to pulmonary tuberculosis had actually been caused by lung cancer, the death rate would have been 9.5 per 100,000. The increase in lung cancer mortality would then have been 2-fold instead of 26-fold. If the diagnostic error had been as little as 5 per cent, the increase between 1914 and 1950 would have been only 4-fold.

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Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

The same postulation applied to white females would have resulted in no increase in lung cancer mortality between 1914 and 1950 if the diagnostic error had been 10 per cent and less than 2-fold if the error had been 5 per cent.

The effect of faulty certification of all respiratory diseases, combined, may be summarized as follows. If 5 per cent of the cases so certified had actually died of lung cancer, the increase in lung cancer mortality among males over 35 years of age would only have been 2-fold between 1914 and 1950; among females, the mortality trend would have been reversed with more females dying of lung cancer in 1914 than in 1950. At the 3 per cent level of error, the increase among males would have been 3-fold and, among females, there would have been no increase.

Experienced physicians will find little difficulty in postulating an error of the magnitude of 10 per cent in the clinical diagnosis of respiratory diseases, particularly, in an era devoid of x-ray examination, bronchoscopy, and thoracotomy. Large scale autopsy studies (174) previously referred to showed an error of more than 60 per cent in the diagnosis of lung cancer when all the modern facilities for the detection of the disease were readily available.

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The Effect of Revisions of Classification

Until relatively recently, the various rubrics assigned to lung cancer in the Manual of International List of

Source: https://www.industrydocuments.ucsf.edu/docs/nynk0000

of Causes of Death made comparisons of mortality rates exceedingly difficult if not impossible. Authoritative statements that the death rate from lung cancer increased in white males from 3.9 per cent in 1930 to 35.4 per cent in 1960 and in non-white males from 1.6 per cent in 1930 to 33.8 per cent in 1960 call for circumspect interpretation. A true evaluation of the mortality data prior to 1950 requires consideration of not only the limited facilities available for diagnosis but also the difficulties of statistical comparability because of the decennial revisions of the code of classification.

Between 1914 and 1920, the classification of deaths ascribed to cancer of the respiratory system was based on the 1909 revision of the International List of Causes of Death, supplemented by subtitles added by the United States Bureau of Census. In this classification lung cancer was listed under the ambiguous title, "Cancer and other malignant tumors of other organs or of organs not specified" and was placed in category 45B which also included cancer of the anterior mediastinum, lung, mediastinal gland, mediastinum, pleura, bronchi, lung and pleura. In classification 45X, cancer of the bronchi was placed in the same group with cancer of the accessory sinus, antrum, posterior nares, and trachea. The code was revised in 1920 and a different calssificatiоn was used between 1921 and 1929 with titles 49B and 49X corresponding to titles 45B and 45X of the 1909 revision. The list was revised again in 1929 and the new titles were used between 1930 and 1938. In this revision

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cancer of the respiratory system became a specific category for the first time and lung cancer was listed under items 47B and 47C. The title of 47B referred to cancer of the lungs and pleura and included subtitles of cancer of the anterior mediastinum, lung, mediastinal gland, mediastinum, and pleura. The title 47C referred to cancer of other respiratory organs and included cancer of the bronchi, nasal cavity, nasopharynx, nostril, posterior nares, and trachea.

The fifth revision of the international code occurred in 1938 and was used between 1939 and 1948. Title 47 referred to cancer of the respiratory system and for the first time included a subtitle 47 (c) with separate designations for bronchogenic carcinoma and cancer of the bronchus. There was also a subtitle 47 (d) for cancer of the lung and pulmonary cancer; a subtitle 47 (e) for cancer of the pleura; and a subtitle 47 (f) for cancer of the mediastinum and unspecified sites. To further add to the confusion, there was also a title 55 (e) for cancer of other and unspecified organs that included designations for cancer of the chest, thoracic cavity and thorax. It is very apparent from the profusion of terminology that the authors of the international code of classification had very little knowledge of the pathogenesis of lung cancer nor were they even aware that bronchogenic carcinoma and lung cancer were the same disease. The greatest indictment against the classification is that for decades it did not even recognize bronchogenic carcinoma as a specific entity thereby discouraging its certification as

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a primary cause of death. The term, bronchogenic carcinoma, was introduced for the first time in 1939 and, in the succeeding decade, the crude death rate increased more than 3-fold.

The sixth revision of the International List of Causes of Death was made in 1948 and has been in use since 1949. This revision was a major step toward clarification of lung cancer mortality but failed to differentiate entirely between primary and secondary lung cancer. Title 162 refers to primary cancer of the bronchus, lung, pleura and trachea. Title 163 refers to the same categories unspecified as to primary or secondary origin. Title 164 refers to cancer of the mediastinum and thoracic organs and title 165 refers to secondary cancer of the bronchus, lung, mediastinum, pleura, thorax, trachea, and respiratory organs not otherwise specified.

A seventh revision of the international classification is expected to be implemented in 1968. In this nomenclature, title 162.1 will include only primary cancer of the bronchus and lung and title 197 will include secondary lung cancer. Whether this classification will contribute to further confusion of mortality data or further clarification will depend on the interest of clinicians and pathologists in differentiating between primary and secondary lung cancer. In the previcus classification the category, 163, included lung cancer unspecified as to whether primary or secondary. In the contemplated revision, if the death certificate fails to specify secondary lung cancer, the case will be automatically listed as

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primary lung cancer thereby artificially increasing the incidence of primary lung cancer. Inasmuch as the differentiation between primary and metastatic lung cancer may not be possible without autopsy, the new classification may create as many problems in statistical accuracy as it solves.

Another factor which contributed to the obscurity of lung cancer mortality data was the set of regulations governing multiple causes of death (207) (208). Prior to 1949, when death certificates listed two or more sites of cancer, the presumptive primary site was arbitrarily coded in the vital statistics. The 1925 edition of the Manual of Joint Causes of Death specified that when lung cancer coexisted with cancer of the digestive tract, buccal cavity, female genital organs, breast, or skin, the latter sites were to be given precedence and tabulated as the primary lesion. The 1933 and 1939 editions of the manual contained a slight revision in favor of lung cancer —— cancer of the skin when reported jointly with lung cancer was no longer classified as the primary disease. Mortality data on lung cancer was therefore influenced for more than 3 decades by predetermined rules of tabulation having no bearing, whatsoever, on the true prevalence of the disease.

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The Decline in the Rate of Increase

In discussing lung cancer mortality trends it should be emphasized that the term, lung cancer, is used merely for expediency and that what is actually under comparison is a

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group of rubrics under the general heading of "cancer of the respiratory system other than larynx". Deaths attributed to bronchogenic carcinoma prior to 1930 are unidentifiable. There are many limitations of the available statistical data (209) but the overall trend of lung cancer mortality follows a pattern that is clinically significant. The increase in lung cancer deaths has been viewed with alarm with dire extrapolative forebodings of skyrocketing future death rates. In actuality, the trend of lung cancer mortality has been far more characteristic of diagnostic acumen than of epidemic spread. For more than three decades there has been a progressive decline in the rate of increase tending toward the same stabilization that occurred in other cancers in which diagnostic techniques have remained unchanged for many years.

Statistical studies by Dorn (210), Gover (211), Gilliam, et al. (212), Gordon, et al.(213) and Milmore (204) show that the greatest increase in lung cancer mortality occurred during the early decades of this century and that the rise began simultaneously for all age groups. In 1914, when the registration area comprised 67 per cent of the total population of the United States, there were 371 lung cancer deaths reported with an adjusted standardized death rate of 0.66 per 100,000. Between 1914 and 1930-1932, the age adjusted mortality rate for white males increased 393 per cent, or about 23 per cent annually. The corresponding increase for white females was 228 per cent, or about 13 per cent annually. Since then, there has been a progressive increase in the total number of lung cancer deaths but

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there has been a consistent decline in the rate at which this has occurred.

In the period, 1930-1932, the adjusted death rate among white males was 4.23 per 100,000; in the period 1939-1941, the death rate was 10.00 per 100,000 in the period 1951-1953, the death rate was 24.43 per 100,000 and in the period 1957-1958, the rate was 33.22 per 100,000. Concomitant with the steady rise in death rate, there also occurred a gradual lowering of the rate of increase during successive periods. Between 1930 and 1935, the annual increase was 10.2 per cent; between 1939 and 1944, the annual increase was 7.0 per cent; between 1954 and 1958, the annual increase was 5.0 per cent, less than half prevailing three decades previously. A similar phenomenon was observed among white females. The adjusted death rate rose from 2.34 per 100,000 in the period 1930-1932 to 5.24 per 100,000 in the period 1957-1958 but the rate of increase declined from 5.6 per cent annually between 1930 and 1935 to 2.0 per cent annually between 1954 and 1958.

Correlation of death rates with age distribution reveals that the major component of the increase in lung cancer was contributed by persons in the 6th decade and older. The rate of increase is declining for all age groups but is more marked in the younger than in the older age groups. This trend is compatible with greater clinical experience in diagnosing lung cancer since the disease occurs predominantly in the older age groups. Among females the declining rate of increase is even more

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striking than that shown by the males and has been fairly constant for all age groups. This, too, is a reflection of increased clinical experience which has shown that lung cancer is chiefly a disease of males. Studies of the non-white population are limited but the available data are informative. The lung cancer mortality rates recorded for the non-white population in 1930 were far lower than those of the white population but increased rapidly thereafter almost achieving equality by 1958. This is consistent with the marked improvement in medical facilities available to the non-white population in recent years. Since 1950, the rate of increase has also been declining for the non-white population.

The declining rate of increase in clinically diagnosed lung cancer followed a pattern similar to that observed when the diagnosis was established only at autopsy. Corresponding to the period of expanding knowledge of the pathology of the disease, there was a marked rise in autopsy incidence followed by a decline in the rate of increase. At the Moabit Hospital in Berlin, Wahl (214) found a 300 per cent increase in the ratio of lung cancer to all cancers between 1917 and 1923; the following year the rate of increase had declined to 17 per cent. Schonherr (215) reported similar findings at the Pathologic Hygienic Institute of Chemmitz. Between the periods 1898-1916 and 1919-1922 there was a 110 per cent increase followed by a decline to 24 per cent in the next four years. Materna (216), at the Troppau Pathologic Institute found the increase of lung cancer among all

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cancers to be 240 per cent between the periods 1912-1914 and 1915-1917; between the latter period and 1921-1923, the increase was only 12 per cent. Schlesinger (217) reported an increase of 120 per cent at the Leipzig Pathologic Institute between the periods 1900-1906 and 1914-1918; between 1914-1918 and 1924-1929, the increase was 18 per cent. At the Prague Pathologic Institute, Holzer (218) found the increase of lung cancer among all cancers to be 190 per cent between the periods 1895-1899 and 1905-1909; 110 per cent between 1905-1909 and 1915-1919; and 66 per cent between 1915-1919 and 1920-1924. Maxwell and Nicholson (219) found an increase of 100 per cent at the St. Bartholomew's Hospital between the periods 1884-1888 and 1894-1898 and no increase between the latter period and 1904-1908.

Claude Bernard's dictum of looking beyond the statistical data is most applicable in evaluating lung cancer mortality. The progressive decline in the rate of increase suggests that the image of a lung cancer epidemic is an illusion created by the magic of numbers. The rise from 2,357 lung cancer deaths in 1930 to 45,838 in 1964 seems, at first glance, to be irrefutable proof of an absolute increase. However, if the rise is studied by lustrums there emerges a pattern completely compatible with the concept that the increase was not real but the effect of improved diagnostic facilities. Between 1930 and 1935, lung cancer deaths increased 79 per cent; between 1935 and 1940, the increase was 68 per cent; between 1940 and 1945, the increase was 53 per cent; between 1945 and 1950, the increase rose to

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67 per cent but fell again between 1950 and 1955 to 46 per cent; between 1955 and 1960, the increase was 36 per cent; and between 1960 and 1965, the increase was only 34 per cent.

Confirmation of the peculiar trend in lung cancer mortality is available from sources other than the official national statistics. A study of Metropolitan Life Insurance Company policyholders by Dublin and Lotka (220) showed that for white males over 45 years of age, the age standardized death rate from lung cancer rose from 3.4 per 100,000 in 1917 to 21.2 per 100,000 in 1935. For all white males (1-74 years) the increase was from 0.9 per 100,000 in 1917 to 4.7 per 100,000 in 1935. The data for males over 45 years are more significant inasmuch as lung cancer occurs predominantly in older age groups but both categories showed annual increases of approximately 10 per cent. For white females, over 45 years of age, the age standardized death rate rose from 2.7 per 100,000 in 1917 to 7.6 per 100,000 in 1935 and, for all females, from 0.7 to 1.9 per 100,000. The annual rate of increase for both categories was approximately 5.5 per cent. The statistical data from this particular segment of the population paralleled the national census figures, again emphasizing that the highest rates of increase in lung cancer mortality occurred paradoxically during the period of growing awareness of the disease rather during the later era of sophisticated diagnostic facilities.

There are no lung cancer mortality statistics available for New York State prior to 1931 when 615 cases were

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reported. In 1935, there were 1,006 lung cancer deaths representing an increase of 64 per cent. In 1940, there were 1,440 deaths with an increase of 43 per cent in the previous lustrum. Between 1945 and 1950, the increase in lung cancer deaths was 33 per cent. In 1965, there were 5,429 lung cancer deaths but the increase between 1960 and 1965 was down to 22 per cent. The trend of lung cancer mortality in New York State is similar to that of the nation and, because of the greater availability of diagnostic facilities, characterizes the decline in the rate of increase even more vividly.

The leveling off of the increase in lung cancer mortality is not a unique experience limited to the United States but has also been noted by Clemmesen (221) in Denmark and Springett (222) in England and Wales. In the latter study, there were three times an many lung cancer deaths in 1963 as in 1946 but the increase was confined to the older age groups. Under 45 years of age there was no increase in lung cancer deaths; in the age group 45-54 years, the number of deaths increased but the proportion for the age group decreased; in the age group 55-64 years, the number of deaths remained unchanged. There was an increase in the number of deaths for ages over 64 years with the proportion rising from 24 to 34 per cent; over 75 years of age, the increase was from 6 to 13 per cent.

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It is impossible to reconcile a declining rate of increase in lung cancer mortality with the epidemic concept. The deceleration of the rate of increase implies that there has been

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a relatively fixed prevalence of the disease in the population and that expansion of interest and diagnostic facilities has resulted in the recognition of a greater number of cases each year leaving proportionately fewer cases undiagnosed. The trend toward progressive decline of the rate of increase is crystal clear and, if unabated, will ultimately produce a standardization of the age adjusted mortality rate of lung cancer even though the total number of cases may continue to rise because of the increasing longevity (223) of the population. It must also be emphasized that while improved diagnostic techniques yield more cases of lung cancer, they also tend to eliminate the erroneously diagnosed cases of pulmonary metastases that simulate bronchogenic carcinoma.

The epidemic concept of the rise in lung cancer mortality has carried with it the implication that the increase was the direct result of the increased consumption of cigarettes. Observations of Gilliam (224) made more than a decade ago are still very applicable to the subject, "It is clear that this hypothesis in its entirety is untenable if the recorded increase is an artifact due to appreciable changes in diagnostic accuracy".

V THE BIOLOGIC FEATURES OF LUNG CANCER

The predilection of lung cancer for males was attributed by the Surgeon General's Advisory Committee to heavier smoking habits and presented as evidence incriminating cigarettes. The absurdity of this assertion becomes readily apparent when it is realized that lung cancer was predominantly a disease of males

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when cigarette smoking was a rarity. Furthermore, the prodigious smoking of females during the past 4 decades has had no effect on decreasing the disparity of sex distribution.

Male Predominance

The affinity of lung cancer for males is a biologic characteristic of the disease. Sex predilection occurs commonly in a variety of diseases and an excellent illustration is cancer of the breast which occurs preponderantly in females. There were a great many studies of lung cancer during an era in which cigarette smoking was virtually non-existent and all showed a remarkable consistency in sex distribution. Hare (95), in a study of lung cancer covering the period 1830 to 1880, found 90 cases in males and 33 cases in females. Adler's (116) collected series of cases spanned the years 1842 to 1911 and included 269 males and 93 females. In a report of the experiences of the teaching hospitals in Great Britain between 1894 and 1918, Passey (225) found 579 cases of lung cancer in males and 182 cases in females. In 1892, Harris (30) reported on a combined study of St. Bartholomew's Hospital and the City of London Hospital for Diseases of the Chest and found that lung cancer occurred three times as often in males as in females. Similar ratios of 3:1 favoring the male were reported from Germany by Passler (77), Riechelman (226), Briese (112), and Karrenstein (115) during the late 19th and early 20th centuries. In the United States, King (83) found a 4:1 ratio in Boston covering the period, 1875-1914. Weller (227) who

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was among the first American pathologists to become interested in lung cancer also found a 4:1 ratio in a collected series of cases between 1878 and 1912.

Despite the variety of the sources of the material studied, there was unanimous agreement on male predilection of the disease before the era of cigarette smoking. It is also of significance that many of the autopsy reports in the 19th century and early 20th century revealed sex ratios as high or higher than those found in recent studies. Wolf (105), reported a 6:1 ratio from the Dresden municipal hospitals for the period, 1885-1884. Eichengrun (114) found a 6.4:1 ratic in Cologne between 1902 and 1919. Rau (228) found a 6.5:1 ratio in Dresden-Friedrichstadt between 1909 and 1914. Feilchenfeld (100) reported a 10:1 ratio in Berlin between 1894 and 1900 and in Leipzig, Lenhartz (82). found a 13:1 ratio.

Inasmuch as lung cancer is predominantly a disease of males, improvements in diagnostic accuracy resulted in proportionately more cases detected in males and a progressive rise in the sex ratio. This phenomenon was already apparent in the early decades of the 20th century when most cases were diagnosed by autopsy and became even more obvious when the disease began to be diagnosed clinically. At the Moabit and Urban Hospitals in Berlin, Peters (111) noted a 3:1 ratio between 1905 and 1908 and a 5:1 ratio in the same institutions between 1917 and 1922. Since 1930, lung cancer certification without autopsy has increased manifold. The early reports showed the distribution of the disease

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to be almost equal between the sexes but, as clinical diagnostic accuracy improved, male predominance became very evident paralleling the autopsy reports of the 19th and early 20th centuries. An excellent illustration of the relationship between diagnostic accuracy and the sex ratio was provided by Clemmensen and Busk (229) who observed that in Denmark, between 1936 and 1945, the overall ratio was 2.4:1 whereas in a special chest clinic in Copenhagen, the ratio was 7.2:1.

The effect of diagnostic accuracy on the sex distribution of lung cancer is also emphasized in the observations of Ibrahim (230) who found, in 1954, a sex ratio of 9:1 in non-cigarette smokers at the Dacca Medical College in East Pakistan where pulmonary diagnostic facilities had been recently established. Among the lowest sex ratios found within the past decade was a report by Farago (231), from Papau and New Guinea covering the period 1958-1962. In those regions of the world, cigarette smoking is widespread but facilities for the diagnosis of lung cancer are still very limited resulting in a sex ratio of only 4:1.

During the past 35 years there has been a progressive rise in the sex ratio in the United States lung cancer mortality statistics. In 1930, there were 1,818 lung cancer deaths reported in males and 1,019 in females giving a ratio of 1.8:1. During the succeeding decade there was an upsurge of interest in the disease and facilities for diagnosis became more available. This was reflected in both an increase in lung cancer mortality and in the sex ratio. In 1940, there were 6,057 male

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deaths and 2,029 female deaths giving a ratio of 3:1. Between 1940 and 1950, advances in diagnosis were even more striking, particularly, the use of exploratory thoracic surgery as a diagnostic tool and the increasing utilization of the Papanicolaou technique for sputum and bronchial aspirate examination. In 1950, there were 14,922 male lung cancer deaths and 3,391 female lung cancer deaths, giving a sex ratio of 4.4:1. During the next decade it was very evident that the increase in lung cancer mortality was chiefly confined to males. In 1960, there were 30,800 male deaths and 5,000 female deaths giving a sex ratio of 6.2:1.

Lung Cancer in Females

The prodigious increase in cigarette consumption by females for more than 4 decades has not been reflected in a corresponding increase of lung cancer. A survey (232) of smoking patterns in 1955 by the United States Bureau of the Census revealed that approximately 46,000,000 persons had been regular cigarette smokers and, of these, 15,000,000 were females over 18 years of age. The survey acknowledged that it had underestimated cigarette consumption by 15 per cent on the basis of tax data and common observation suggests even a greater margin of error. Current estimates point to more than 70,000,000 cigarette smokers with a proportionate increase among females. If cigarette smoking is a potent carcinogenic agent it should have affected lung cancer mortality by this time resulting in an equalization of

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the sex ratio which in 1964 was 6.4:1. Diagnostic facilities have been equally available to both sexes for many years.

The lung cancer death rate in females increased from 1.5 per 100,000 in 1930 to 7.1 per 100,000 in 1964 but still remains far below the rate of 41.4 per 100,000 for males (233). It is inconceivable for such a difference in lung cancer mortality to exist if cigarette smoking was a significant causal factor in lung cancer. The proponents of the smoking-cancer hypothesis reconcile the disparity with claims that females have begun to smoke relatively recently and that eventually the lung cancer rates will equal those of males. The truth is that females have been smoking for more than 40 years and that sufficient time has elapsed for the alleged carcinogenic action of tobacco to express itself, if indeed, it exists at all. Between 1959 and 1964, the total increase in female lung cancer deaths was only 2,400, averaging less than 500 per year for the period. The corresponding increase for male lung cancer deaths was 11,500. With so many millions of persons of both sexes smoking cigarettes regularly, parity in lung cancer mortality would have been reached a long time ago if tobacco was a causal factor. Observations in both the pre-cigarette and cigarette smoking eras have shown that the female is resistant biologically to lung cancer although vulnerable to other types of malignancy.

There is increasing evidence (232-234) that many of the cases diagnosed in females as primary lung cancer are, in actuality, metastatic cancers from the breast and genital organs.

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The affinity of the lung for secondary growths from these organs is well established. In 1964, there were approximately 45,000 deaths reported from cancer of the breast, uterus, and ovary of which 26,000 deaths were attributed to cancer of the breast alone. With more than two-thirds of breast cancers and one-third of genital cancers metastasizing to the lung, there is created a vast potential for diagnostic error, particularly, in cases of solitary pulmonary metastases with occult tumors in the primary site. (262)

Greater histologic experience in the diagnosis of pulmonary tumors will manifest itself in subsequent years by more discriminatory diagnoses of lung cancer in females. There is already an inclination of this trend in the 1964 lung cancer mortality data. Of the 19,651 cases certified as primary lung cancer, there were 17,134 males and 2,517 females, giving a ratio of 6.8:1. In the 26,066 cases not certified as to primary or secondary origin there were 21,684 males and 4,382 females giving a ratio of 5:1. (See Table I, page 64 (a)).

Age Distribution

Lung cancer occurs predominantly in the older age groups with the majority of cases in the 5th, 6th, and 7th decades of life. The disease is unusual below the age of 40 and a rarity below the age of 30. Simons (234), in a collected series of more than 5,000 cases found that 80 per cent had occurred between 40 and 70 years of age. This distinctive age distribution was noted

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TABLE I

LUNG CANCER MORTALITY

Classification of Cases According to 7th Revision of International Code

Lung Cancer	1959	1960	1961	1962	1963	1964
Classification No. 162.1 (Specified as primary)	17,042	18,342	19,462	18,749	18,868	19,651
Classification No. 163 (Unspecified as to whether primary or secondary)	17,139	18,978	19,467	22,510	24,569	26,066

It is evident from Table I that the major portion of the rise in lung cancer mortality between 1959 and 1964 was in classification No. 163 which showed an increase of 8,927 cases (52.0 per cent). The increase in classification No. 162.1 was only 2,609 cases (15.3 per cent). Between 1961 and 1964 the increase in classification No. 162.1 was negligible whereas, in classification No. 163, there were 6,599 additional cases. These figures are indicative of greater discrimination in the diagnosis of primary lung cancer by the certifying physicians. The increase in classification 163 connotes greater awareness of the possibilities of metastatic lung cancer simulating bronchogenic carcinoma. It has been stated by the advocates of the epidemic concept that the failure to specify primary lung cancer on death certificates is merely an oversight. According to this misguided interpretation the lung cancer mortality figures since 1961 imply a steady increase in laxity in the medical profession inasmuch as the apparent oversight is getting progressively larger.

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in the 19th century (77,31,105,157) in the absence of cigarette smoking and also in recent decades in the era of widespread cigarette consumption (122,173,235,236). The relationship between longevity of the population and the incidence of lung cancer is therefore very significant.

During the past 50 years there has been a spectacular increase in the life span for all subdivisions of the population (237). In the period 1900-1902, the life expectancy at birth for white males was 48.23 years; in 1959-1961, the life expectancy had increased to 67.55 years. The life expectancy for white females was 51.08 years in the period 1900-1902 and 74.19 years in the period 1959-1961. This increase in the life span was even more striking in the non-white population. Non-white males had a life expectancy of 32.54 years in 1900-1902 and this increased to 61.48 years for the period 1959-1961. During the same interval the life expectancy for non-white females rose from 35.04 years in 1900-1902 to 66.47 years in 1959-1961.

Comparative studies on mortality rates present problems because of the limited number of states in the registration area in the early part of the century. Some degree of accuracy may be ascertained by comparing the life span per 100,000 persons over a period of several decades. In 1900-1902, of every group of 100,000 white males born alive, only 46,452 reached 60 years of age. Sixty years later, the statistical picture was entirely different. In 1959-1961, there were 75,485 white males

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out of every 100,000 who reached 60 years. The corresponding increase among white females was from 50,752 in 1900-1902 to 86,339 in 1959-1961. Improvements in medical care, greater availability of diagnostic and therapeutic facilities, and higher economic standards of living were reflected in increased longevity of the non-white population. Whereas in the period 1900-1902, there were only 24,194 non-white males who attained 60 years of age, in 1959-1961, the number had increased to 61,669. The corresponding increase among non-white females was from 27,524 to 69,941.

The population of the United States is now considerably older than that in existence in the first decade of the 20th century. Within 50 years, the average duration of life increased 19.32 years for white males, 23.11 years for white females, 28.94 years for non-white males, and 31.43 years for non-white females. Current statistical reports (238) show no indication of abatement of the trend toward longer life expectancy. For 1965, the estimated expectation of life at birth was 70.2 years for the total population. It is very evident that, regardless of any hypothetical etiologic considerations, the total number of potential subjects for lung cancer has increased by many millions during the past half century. The inherent biologic characteristic of the disease to develop in older age groups will therefore result in the occurrence of more cases in future years as proportionately more of the population reaches the later decades of life.

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Age at Onset

The predilection of lung cancer for the older age groups has a definite relevancy to etiologic considerations. If cigarette smoking produces a cumulative carcinogenic effect over a period of years then the segment of the population that began cigarette smoking in the early teen ages should develop lung cancer at a far younger age than those persons who began smoking at 30 to 40 years of age. There is also to be considered the effect of heavier smoking habits. Cigarette consumption per capita was only 50 per year at the turn of the century and by 1960 it had increased to 4,000 per year. It would seem reasonable to expect that if cigarettes were a carcinogenic hazard to health, the increased consumption would have resulted in a lowering of the age of occurrence of lung cancer. The fact is that neither the age at onset of smoking nor the number of cigarettes consumed has had any appreciable effect on the age of distribution of lung cancer which has remained a constant biologic feature since the disease was described 150 years ago.

In 1962, Passey (239) reported an investigation of 415 males with lung cancer to determine the effect of smoking on onset of the disease. The results showed that lung cancer had been acquired at approximately the same age regardless of whether smoking had been started at 6 years or at 41 years of age. Equally significant was the finding that the number of cigarettes smoked daily did not affect the age at onset; in both the light smokers

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and the heavy smokers the disease had developed during the same decades of life. In 1965, Pike and Doll (240) studied a group of British doctors with lung cancer equating the consumption of cigarettes with the average age at death. Among the doctors who began to smoke at 17 years of age, the average age at death was 71.8 years for the light smokers and 69.3 years for the heavy smokers. The duration of smoking was also equated with the average age at death. Among those who smoked 15-24 cigarettes daily since the age of 17 years, the average age at death was 70.5 years; among those who consumed the same amount but began to smoke at 32 years of age, the average age at death was 75.0 years; and among those who started to smoke at 42 years, the average age at death was 78.0 years. The differences in age at death between the groups may be statistically significant but have little clinical importance because of the variety of conditions that contribute to mortality in the 8th decade of life.

Experimental Confirmation

A statistical association between two variables is not proof of a causal relationship. It is regrettable that this obvious axiom should have eluded the Surgeon General's Advisory Committee so completely. There is a very high degree of correlation between automobile accidents and being fully clothed but the latter is in no way responsible for the former. A statistical association, per se, has little meaning unless there is also established a biologic or physical relationship between the two

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phenomena. In the case of the smoking-lung cancer association, no definite biological confirmation has been obtained despite the numerous attempts to produce bronchogenic carcinoma in the experimental animal.

Most of the experiments have involved mice because of the tendency of certain strains to develop lung tumors spontaneously. Uniformly negative results were obtained by Campbell (241) in 1936, Lorenz (242) in 1943, Essenberg (243) in 1952, and Leuchtenberger (244) in 1960. In not a single instance had the disease been produced experimentally by exposure to tobacco smoke. Another form of experimentation involved the direct application of tobacco extracts or smoke condensates. This, too, could not produce bronchogenic carcinoma (245,246) except for one glaring exception (247) in which the disease was produced in 1 out of 130 experimental animals. In the customary appraisal of scientific experiments these findings would be given important consideration in evaluating causal relationships but the Advisory Committee dismissed them as incidental and subtly invalidated the negative results with irrelevant sophistries.

In one section of the Report dealing with the chemical composition of cigarette smoke it is stated that polycyclic aromatic hydrocarbons are carcinogenic in rodents and that therefore one can reasonably presume that the same substances may also be carcinogenic in one or more tissues in man. The Report then cited evidence that skin cancer can be induced by certain industrial hydrocarbons and concluded that inasmuch as some of

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these substances were present in tobacco smoke, the latter should also be assumed to be carcinogenic. This specious syllogistic reasoning implicating tobacco as a cancer producing substance in man seems a very weak argument when confronted by the many million-years of exposure of the fingers of smokers to tobacco smoke without producing cancer of the skin. The low prevalence rate of lung cancer in smokers also fails to substantiate the thesis that the hydrocarbons in cigarette smoke are carcinogenic in man. In a matched study of 36,975 smokers and an equal number of non-smokers, Hammond (248) found 110 lung cancers in the smokers and 12 in non-smokers. There were 9 times as many cancers in the smokers but the prevalence rate was only 0.3 per cent, or, 1 lung cancer in every 336 smokers. It is difficult to reconcile the alleged carcinogenicity of cigarettes with the failure to produce the disease in 36,863 (99.7 per cent) smokers.

Pathologic Studies

In an attempt to provide a biologic parameter for the statistical association between smoking and lung cancer, the Advisory Committee referred to certain studies (249-251) showing alterations in the epithelial lining of the respiratory tract of smokers. The changes had been found in smokers and also in lung cancer patients and from this the Committee deduced that the changes probably represented precancerous conditions thereby providing the missing link between smoking and lung cancer. Unfortunately, the Committee was unaware that the pathologic findings

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in smokers were located in those parts of the bronchial tubes in which lung cancer seldom develops. The most advanced precancerous changes were found equally distributed among the large and small bronchial tubes whereas it is now well established (252-254) that lung cancer originates predominantly in the smaller bronchi or more peripherally.

The tendency for the alleged precancerous conditions to occur in parts of the lung seldom involved by lung cancer was also observed in a study (255) similar in scope to those cited in the Report. It was found, paradoxically, that the most advanced changes occurred at the bifurcation of the largest bronchi where lung cancer rarely originates and that the pathologic changes were least evident in the smaller bronchi where the disease develops most frequently. A study (256) of the distribution of inhaled smoke also revealed an inverse relationship between the sites of smoke concentration and those of lung cancer origin with the greatest concentration of smoke found below the trachea. It appears from these studies that in those parts of the lung with the greatest concentration of smoke and the most precancerous changes there is found the smallest number of lung cancers.

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It must be emphasized that the alleged precancerous changes observed in the bronchial epithelium of smokers are the same changes that have been observed in patients with inflammatory diseases of the lung for many decades prior to the era of

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widespread cigarette smoking. As early as 1876 it was noted that one of the complications of pneumonia was an atypical growth of cells of the bronchial mucosal lining and similar changes were described in 1895 in tuberculosis (257,105). In 1920, a monograph on the pathology of influenza depicted these changes most vividly (258). The pathologic alterations identified by the Advisory Committee with cigarette smoking occur commonly in a variety of diseases including bronchiectasis, bronchopneumonia, and lung abscess. They represent the natural protective response of the bronchial epithelial cells against trauma and occur in smokers and non-smokers. Newly formed cells proliferate from the germinal layer of epithelium to form a new type of tissue resembling squamous epithelium. These changes are very common and, it they led to lung cancer, the incidence of the disease would be many times greater.

The Report also identifies certain types of lung cancer with smoking and other types with non-smoking according to the classification of Kreyberg, a Norwegian pathologist (259). This concept bolsters the smoking - lung cancer hypothesis but is incorrect in its premise. Recent studies (260) have shown that the histologic types of lung cancer are definitely related to the site of origin in the bronchial tract. The squamous and oat cell carcinomas arise predominantly from the segmental bronchi and the adenocarcinomas arise chiefly from the minute bronchi, or distally. All bronchial epithelium has a common embryologic

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origin and the various histologic types and structural features of lung cancer are determined by the site of origin, degree of differentiation, and environmental surroundings. It was also found that lung cancer occurs predominantly in only a few segments of the lung and uncommonly in the other parts of the lung. It is difficult to reconcile this finding with the smoking hypothesis unless it is assumed that cigarette smoke has a preternatural affinity for these particular areas.

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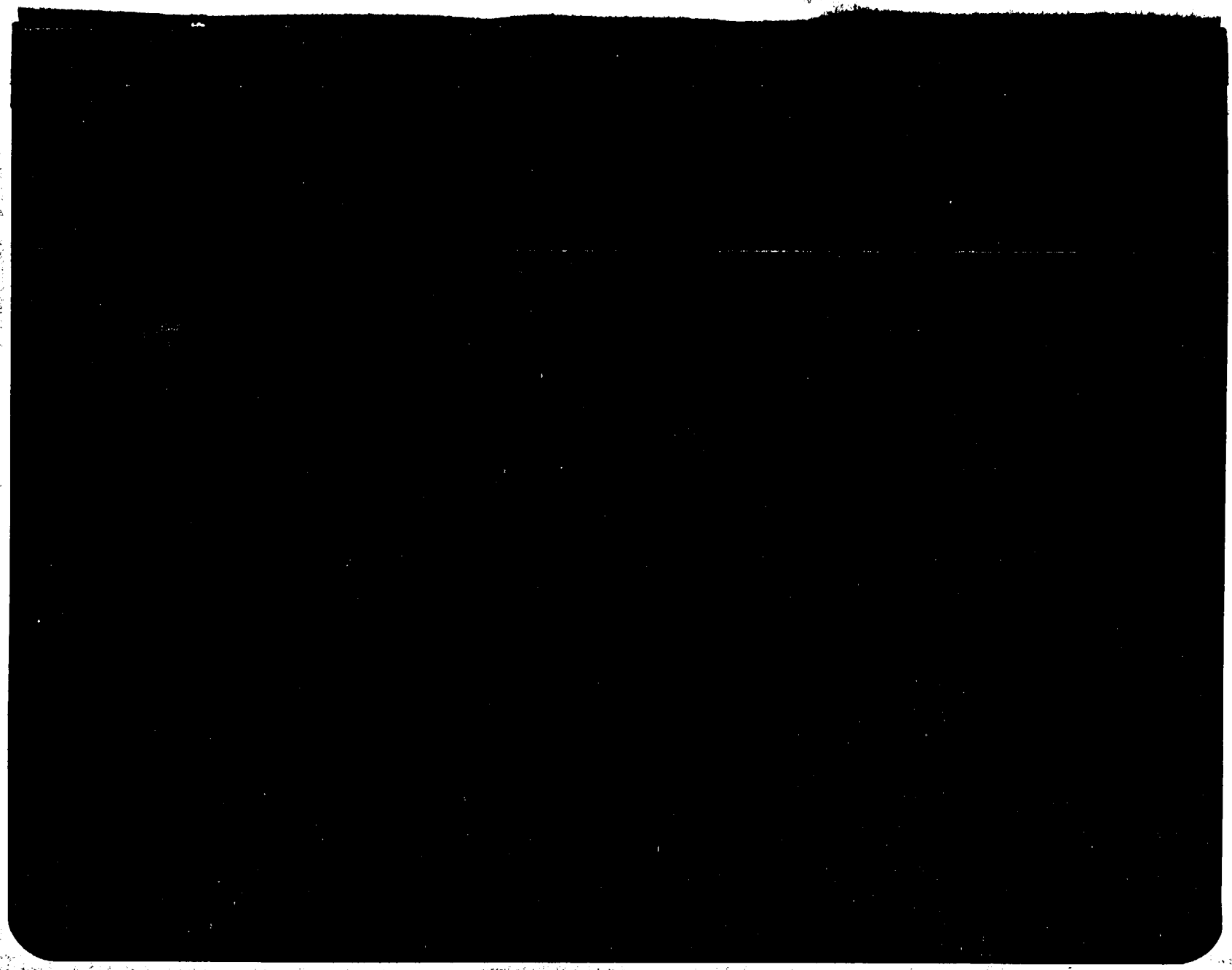

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